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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	10/059,720	VINSON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on th cov r sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-56* is/are pending in the application.

4a) Of the above claim(s) *35,36,41,42,52,53 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-34,37-40,43-51,54 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/19/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 28-56 are pending in the present application.

Applicant's election with traverse of Group II (claims 28-56), drawn to a method of creating or producing a transgenic nonhuman animal or mammal, and the same transgenic nonhuman mammal, in the Response to Restriction Requirement dated 9/15/2003 is acknowledged. Applicants also elected with traverse: (a) Fos protein as the naturally occurring cellular protein, and (b) SEQ ID NO:19 as an amino acid sequence containing in the expressible dominant negative protein to the naturally occurring cellular protein as separate groups (please note that this is not a species election).

The traversal is on the ground(s) that there is a significant overlap in the subject matter between Groups I and II, such that references considered during the examination of the claims of one group likely would be considered during the examination of the other group. An acidically modified nucleic acid binding protein containing an N-terminal extension of acidic amino acid residues is relevant to both Groups, and that the claims of Groups I-II are classified in the same class. This is not found persuasive because the method of creating a transgenic plant of Group I and the method of creating a transgenic non-human animal of Group II are distinct methods, having different starting materials, different method steps and different technical considerations for achieving the end-results. Additionally, the end-results of these methods are distinct products; a transgenic plant (Group I) vs a transgenic non-human animal (Group II). It would be undue burdensome for the examiner to search and/or consider the

patentability of both inventions in a single application because separate searches are required (both patent and literature searches, not merely based on the same classification as argued by Applicant) as the divergent subject matters are recognized for the reasons set forth above.

With respect to the traversal on the requirement to elect a specific sequence corresponding to N-terminal extensions of acidic amino acids and the specific naturally occurring cellular protein, Applicant argue that both the recited sequences and naturally occurring cellular proteins show a common utility (e.g., binding to a nucleic acid sequence) and a substantial structural feature essential to that utility (e.g., nucleic acid binding domains). This is not found persuasive because apart from the generic property of binding to a nucleic acid sequence via a nucleic acid binding domain, each recited naturally occurring cellular protein and each recited amino acid sequence has a distinct amino acid sequence without a substantial common core structure between one and the others, as well as different biochemical property/activity one from the others (e.g., Fos from Jun, GCN4, VBP, GBF-1, opaque, DBP, CHOP-10, CREB, C/EBP, PAR, c-myc, max, mad and others). It should be further noted that the transgenic art is unpredictable with respect to attainment of the desired phenotype, and therefore the operation, function and effects using different DNA molecules encoding distinct dominant negative acidically modified proteins to different naturally occurring cellular proteins are different and distinct. Moreover, a search of more than one of the listed SEQ ID NOs represents an undue burden on the Patent and Trademark Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 35-36, 41-42, 52-53 and 55 are withdrawn from further consideration because they are drawn to non-elected inventions.

Accordingly, claims 28-34, 37-40, 43-51, 54 and 56 are examined on the merits herein.

Priority

Upon review of the specifications of the provisional applications, 60/018,496 and 60/001,654, filed on 5/29/1996 and 7/31/1995, respectively; and comparison with the specification of the present application, it is determined that the specification of the provisional application 60/001,654 is not enabling for the make and use of the instant elected invention. The specification of the provisional application 60/001,654 has no literal written support for SEQ ID NO: 19. Accordingly, with respect to the elected invention, the instant claims are given a priority date of 5/29/1996.

Claim Objections

Claims 34, 37, 40, 51, 54 and 56 are objected to because they contain non-elected embodiments. Appropriate correction is required.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-34, 37-40, 43-51, 54 and 56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

With respect to the elected invention, Applicant's invention is drawn to a transgenic non-human mammal all of whose germ cells and somatic cells, particularly adipose tissue cells, contain a recombinant acidic dominant negative polynucleotide sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, wherein the expression product of said acidic dominant negative sequence stably dimerizes or multimerizes with a normal cellular protein, for the instant case a Fos protein, and a method for producing the same. Applicants' invention is also directed to a method of creating a transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein using an isolated DNA molecule encoding an acidically modified nucleic acid binding protein containing

an N-terminal extension of acidic amino acid residues that allows said acidically modified nucleic acid binding protein to dimerize or multimerize with the Fos protein. The claims encompass a transgenic non-human mammal having any phenotype as long as it contains a gene encoding an expressible dominant negative protein of the present invention to a Fos protein, and said dominant negative protein is expressed in cells, particularly adipose tissue cells, of said transgenic mammal; and the methods for producing the same.

Apart from the disclosure of a transgenic mouse whose genome comprises a DNA sequence encoding the dominant negative 3heptadF C/EBP, operably linked to the adipose fatty acid-binding protein 422/aP2 promoter, exhibits a "skinny" phenotype, the specification fails to describe any transgenic mouse whose genome comprises a DNA sequence encoding an expressible dominant negative protein to a Fos protein (e.g., 0-hep-Fos, 1hep-Fos, 2hep-Fos or 4hepFos) having an associated desired or useful phenotype, let alone any phenotype. Nor do Applicants provide a sufficient representative number of species of a transgenic mammal or animal containing a gene encoding an expressible dominant negative protein to a Fos protein with a useful phenotype as encompassed within the scope of the presently claimed invention. Additionally, the state of the art of transgenesis at the effective filing date of the present application (5/29/1996) was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of a transgene and the result of such incorporation to cause a desired phenotype.

The claimed invention as a whole is not adequately described. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure, particularly any useful phenotype associated with any transgenic non-human animal or mammal whose genome containing a gene encoding an expressible dominant negative protein to a Fos protein of the present invention, and a method for producing the same and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 28-34, 37-40, 43-51, 54 and 56 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, claims 28-34 and 37 are directed to a method of creating a transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein by introducing into a cell of the non-human animal an isolated DNA molecule encoding an acidically modified nucleic acid binding protein containing an N-terminal extension of acidic amino acid residues, said acidic N-terminal extension allowing the acidically modified nucleic acid binding protein to dimerize or multimerize with a Fos protein. Claims 38-40, 43-51, 54 and 56 are drawn to transgenic non-human mammal whose germ cells and somatic cells contain a recombinant acidic dominant negative polynucleotide sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, wherein the expression product of said acidic dominant negative sequence stably dimerizes or multimerizes with a Fos protein, preferably the dominant negative protein is expressed adipose tissue cells of said transgenic mammal; and a method for producing the same.

Pertinent to the elected invention, the specification teaches by exemplification the preparation of a transgenic mouse whose genome comprises a DNA sequence encoding the dominant negative 3heptadF C/EBP, operably linked to the adipose fatty acid-binding protein 422/aP2 promoter, and said transgenic mouse displays a "skinny" phenotype. The evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the presently elected invention for the following reasons.

(1) The breadth of the claims.

With respect to the elected invention, claims 28-34 and 37 encompass a method of creating any transgenic non-human animal (non-human mammals as well as non-mammal animals) having any phenotype as long as it contains a gene encoding an expressible dominant negative protein to a Fos protein, via the introduction into any cell of the non-human animal an isolated DNA molecule encoding an acidically modified nucleic acid binding protein containing an N-terminal extension of acidic amino acid residues, said acidic N-terminal extension allowing the acidically modified nucleic acid binding protein to dimerize or multimerize with a Fos protein. Claims 38-40, 43-51, 54 and 56 are drawn to any transgenic non-human mammal having any phenotype whose germ cells and somatic cells contain a recombinant acidic dominant negative polynucleotide sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage, wherein the expression product of said acidic dominant negative sequence stably dimerizes or multimerizes with a Fos protein, preferably the dominant negative protein is expressed adipose tissue cells of said transgenic mammal; and a method for producing the same.

(2) The state and the unpredictability of the art. At about the effective filing date of the present application (5/29/1996), the art of transgenesis was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of a transgene (for this instance an expressible dominant negative protein to a Fos protein) and the result of such incorporation to cause a desired phenotype in any animal species. Particularly, the predictability of an anticipated useful phenotype arises from the disruption of a particular gene or suppression the expression of a gene product. Moreadith et al. (J. Mol. Med. 75:208-216, 1997) supported phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discussed that gene targeting at a particular locus is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. reported that gene targeting at the endothelial loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype of abnormal control of blood pressure (See page 208, column 2, second paragraph).

It was also known in the art that the level and specificity of a specific transgene as well as the resulting phenotype of the transgenic mouse are directly dependent on a specific transgene construct. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in a transgene construct, the specificity of transgene integration into the genome are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology 45:57-68,

1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61, last paragraph). Houdebine (J. Biotechnol. 34:269-287, 1994) also discloses that in the fields of transgenic, constructs must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (page 275, col. 1, first paragraph). Furthermore, without evidence to the contrary, transgene expression or behavior is not predictable and varies according to the particular host species, and specific promoter/gene combinations. This observation is supported by Hammer et al. (J. Anim. Sci. 63:269-278, 1986) who reported the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert et al. (Molecular Endocrinology 2:277-283, 1988) reported that a transgenic pig did not develop an expected phenotype of growth during the rapid growth phase, when transfected with a Moloney murine leukemia virus rat somatotropin fusion gene (abstract, page 277). Wall et al. also stated "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 62, first paragraph).

(3) The amount of direction or guidance presented.

As enablement requires the specification to teach how to **make and use** the claimed invention, apart from the disclosure of a transgenic mouse whose genome

comprises a DNA sequence encoding the dominant negative 3heptadF C/EBP, operably linked to the adipose fatty acid-binding protein 422/aP2 promoter, displaying a "skinny" phenotype, the instant specification fails to provide any guidance for a skilled artisan on how to attain any transgenic animal or mammal whose genome comprising a gene encoding an expressible dominant negative protein to a Fos protein, and said transgenic animal or mammal has any useful phenotype. Without any disclosure for such a transgenic animal or mammal having any useful phenotype, one skilled in the art would not know how to use it and for what purposes, particularly in light of the unpredicatability for attaining a desired phenotype in the art of transgenesis as discussed above.

There is no evidence of record indicating that the expressible dominant negative 3heptadF C/EBP is also an effective dominant negative protein to the Fos protein. Baxevanis et al. (Current Opinion in Genetics and Development, 3:278-285, 1993, IDS) have noted that the exact structural rules governing the choice of dimerization partners have not yet been determined, although heterodimers are known to form between Fos and Jun, amongst members of the ATF/CREB family, amongst members of the C/EBP family and **between members of the ATF/CREB and Fos/Jun families**, and that the successful dimerization of bZIP proteins depends upon the ability of both the individual carboxyl-terminal alpha-helices to line up in correct register with one another and generate a symmetric coliled coil (see page 280, col. 2, under the section of specificity of dimerization). Moreover, in a post-filing art Ahn et al. (Molecular and Cellular Biology, 18:967-977, 1998; IDS), it has been reported that dominant negative inhibitors

constructed by fusing a designed acidic amphipathic extension onto the N-terminus of the leucine zipper of Fos, Jun, C/eBP, ATF-2 or VBP **did not block CREB DNA binding activity** (see abstract, and Figure 3).

With respect to claims 28-34 and 37 encompassing a method of creating any transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein, via the introduction into any cell of the non-human animal, the instant specification is not enabled for such a method. Apart from the ES cell approach already known in the art for creating or generating a transgenic mouse, the instant specification fails to provide sufficient teachings and/or examples demonstrating that any transgenic non-human animal containing a gene encoding an expressible dominant negative protein to a Fos protein can be generated using any cell type of the non-human animal. Moreover, with respect to the breadth of the claims encompassing any transgenic non-human animal, it is also well known that the ES cell technology is generally limited to the mouse system, since at the effective filing date of the present application Moreadith et al. note that only "putative" ES cells exist for other species (see Summary on page 214). Seamark (Reprod. Fertil. Dev. 6:653-657, 1994) also supported this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract). Likewise, Mullins et al. (J. Clin. Invest. 98:S37-S40, 1996) stated that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell has been successfully demonstrated" (column 1, first paragraph, page S38). At the effective filing date of the

present application since the prior art did not provide such guidance, it is incumbent upon the instant specification to do so. In the absence of such guidance provided by the instant specification and given the unpredictability of transgenic art as already discussed above, it would have required undue experimentation for one skilled in the art to make and use the presently elected claimed invention.

With regard to the breadth of the instant claims, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues raised above, the unpredictability of the transgenic art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the instant claimed invention.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339 or (571) 272-0776 after 1/13/04.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

GERRY LEFFERS
PRIMARY EXAMINER